REMARKS

Claims 13, 14, and 23-32 were pending in the present application. Claims 14 and 23 have been canceled, without prejudice, claims 13, 24, 29, and 30-32 have been amended, and new claims 33-69 have been added. Accordingly, after the amendments presented herein have been entered, claims 13 and 24-69 will remain pending. For the Examiner's convenience, the currently pending claims are set forth herein in Appendix A.

Applicants submit herewith a "Version with Markings to Show Changes Made," which indicates the specific amendments made to the claims.

Support for the new claims and the claim amendments presented herein can be found throughout the specification, including the originally filed claims. Support for the amendments to claims 31 and 32 and new claims 68 and 69 may be found in the specification at least, for example, page 20, line 28 and at page 14, line 30 through page 15, line 13.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 13-14 and 23-32 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 13-14 and 23-32 under 35 U.S.C. §112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that

> [c]laims 13, 30, 31, 32 and their dependents are drawn to a method for identifying a contraceptive or compound which modulates meiosis, however are rendered vague and indefinite for reciting "said compound" in step d because it is unclear id "said compound" is referring to the test compound of steps a and b, or the selected compound of step c. Applicant may prefer to insert the word "selected" between "said" and "compound" or step d, to more clearly identify which compound is identified as the compounds useful as a contraceptive or modulator of meiosis.

Applicants respectfully traverse the foregoing rejection. However, in an effort to expedite prosecution and in no way acquiescing to the Examiner's rejection, Applicants have amended claims 13 and 30 as suggested by the Examiner. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Furthermore, with respect to claim 30, the Examiner is also of the opinion that this claim "is rendered vague and indefinite for reciting 'modulates' in step c, because it is unclear what activity must occur for the compound to qualify as a contraceptive. For example, does the compound inhibit, stimulate, destroy, or deactivate MSH5."

Applicants respectfully traverse the foregoing rejection. Applicants respectfully submit that the claim language is clear and definite and would be understood by one of skill in the art when read in combination with the teachings of the specification. The meaning of the term "modulates" would have been readily apparent to one of ordinary skill in the art at the time the instant application was filed in view of the teachings of Applicants' specification and the well-established meaning of the term. Modulation, *e.g.,* of MSH5 expression or activity, would have been readily understood by one of ordinary skill in the art to mean either the inhibition of expression or activity or the stimulation of expression or activity. Applicants' specification, at page 14, lines 30-35 identifies "modulators" as compounds which "have a stimulatory or inhibitory effect on, for example, MSH5 expression or MSH5 activity." Accordingly, the meaning of the term "modulation" was well-established in the art at the time of filing of the instant application and its' meaning would have been readily apparent to one of skill in the art in view of Applicants' specification.

However, in the interest of expediting prosecution, and in no way acquiescing to the Examiner's rejection, claim 30 has been amended such that it contains the term "inhibition" rather than the term "modulation." Accordingly, the pending claims comply with 35 U.S.C. §112, second paragraph. Based on the foregoing, Applicants' respectfully request reconsideration and withdrawal of the foregoing rejection.

Rejection of Claims 31 and 32 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 31 and 32 under 35 U.S.C. §103(a) as being unpatentable over Fishel *et al.* (U.S. Patent No. 6,333,153) in view of Winand *et al.* In particular, the Examiner is of the opinion that

> Applicant claims a method for identifying a compound which modulates meiosis in a cell, the method comprising a) contacting MSH5 with a test compound, and b) determining the activity of MSH5 in the presence and absence of the test compound, c) selecting the compound which modulates MSH5 activity, and d) identify the selected compound as a compound that modulates meiosis in a cell. Applicant additionally claims the method wherein a cell expressing MSH5 is contacted with a test compound. Fishel teaches a method for determining if a composition (test compound) affects (or modulates) expression of a gene encoding a MutS homolog (MSH) (col. 9 line 10-15) wherein the MutS homolog may be MSH5 (col. 4 line 35-40). The method comprises administering the test composition (or compound) to a cell containing the MutS homolog (or MSH5) and a cell which does not contain the MutS homolog followed by observing phenotypic effects on the cells to determine if the compound effects (or modulates) MutS homolog activity (col. 9 line 29-45). Fishel does not teach the method wherein the test compound that modulates MSH5 is useful for modulating meiosis. However, Winand teaches that MSH5 is required in normal meiotic crossing over (abstract, p. 69 right column) and encodes proteins which function in meiotic cells (p. 69, right column). Moreover, at the time of the claimed invention, it was known in the art that MSH5 plays a modulating role in meiosis. Therefore, at the time of the claimed invention, it would have been obvious to one of ordinary skill in the art to identify meiosis-modulating-compounds by identifying compounds which modulate MSH5. Moreover, at the time of the claimed invention, one of ordinary skill in the art would have been motivated by Winand to use the methods of Fishel for identifying compounds which modulate MSH5, with a reasonable expectation for successfully identifying compounds which modulate meiosis. Applicant argues that the references do not teach a relationship between MSH5 and meiosis modulation. However, this argument fails to persuade because as disclosed by Winand, it was known in the art that MSH5 plays a crucial role in meiosis, as stated above.

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references renders the claimed invention obvious to the ordinarily skilled artisan at the time of the invention. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

Pending claims 31 and 32, as amended, are directed to methods for identifying candidate compounds useful for inhibiting chromosome synapsis. Applicants have demonstrated in the present application (see Example 1 at pages 18-21 of Applicants' specification) and in subsequent publications (Kneitz B. *et al.* (2000) *Genes Dev.* 14(9):1085-97, provided herewith as Appendix B) that MSH5 is essential for proper chromosomal pairing in prophase I and/or synapsis. Applicants have also demonstrated in the present application that, because of its involvement in chromosomal pairing and/or synapsis, knocking out the MSH5 encoding gene in an animal results in infertility of the animal. Applicants have shown that disruption of meiosis prior to synapsis in *Msh5*$^{-/-}$ mice results in the loss of oocytes, ovarian degeneration, and failure of folliculogenesis in female *Msh5*$^{-/-}$ mice and in the severe disruption of spermatogenesis, depletion of germ cells, and decrease in testicular size in male *Msh5*$^{-/-}$ mice (see, for example, Figures 2-6 and Example 1 of Applicants' specification).

To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, e.g., *Carella v. Starlight Archery,* 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985).

Applying this standard to the references cited by the Examiner, it is clear that the Examiner has failed to meet the burden of providing evidence of a motivating force sufficient to impel a person of ordinary skill in the art to arrive at Applicants' invention. Specifically, Fishel *et al.* fail to teach or suggest any association between MutS homologs, such as MSH5, and contraception or meiosis. Neither do Fishel *et al.* teach or suggest methods for identifying candidate compounds useful as contraceptives or useful for modulating meiosis. Thus, the primary reference of Fishel *et al.* relied upon by the Examiner, fails to teach or suggest the claimed invention.

Furthermore, the secondary reference of Winand *et al.* relied on by the Examiner fails to make up for the above stated deficiencies in the primary reference of Fishel *et al.* Specifically, Winand *et al.* disclose identification of the nucleotide and amino acid sequences of *C. elegans* and human MSH5. Winand *et al.* state that *S. cerevisiae* MSH5 is required for "normal levels of meiotic crossing over" (page 69, right column). Winand *et al.* generally state that, based on only expression data, human MSH5 may be important for a meiosis-specific process like recombination (see page 77, right column). Nowhere do Winand *et al.* teach or suggest that human MSH5 is essential for ***proper chromosome synapsis***. Neither do Winand *et al.* teach or suggest methods for identifying candidate compounds useful for modulating chromosome synapsis in a cell. Thus, Winand *et al.*, in combination with Fishel *et al.* fail to teach or suggest Applicants' invention.

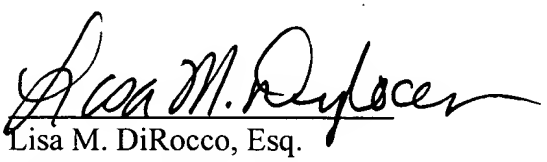
In summary, Applicants respectfully submit that, contrary to the Examiner's assertions, the ordinarily skilled artisan at the time of Applicants' invention would not have been motivated nor have reasonably expected to succeed in arriving at Applicants' invention. For the foregoing reasons, rejection of the claimed invention is believed to be improper and Applicants respectfully request that it be withdrawn.

CONCLUSION

In view of the amendments set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



Lisa M. DiRocco, Esq.
Registration No.: 51,619
Attorney for Applicants

28 State Street
Boston, Massachusetts 02109
telephone: (617) 227-7400
facsimile: (617) 742-4214

Date: **June 2, 2003**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 14 and 23 have been canceled, without prejudice, and claims 13, 24, 29, and 30-32 have been amended as follows:

13. **(Twice Amended)** A method for identifying a candidate compound useful as a contraceptive, comprising:

a) contacting MSH5 with a test compound;

b) determining the activity or expression of MSH5 in the presence ~~and absence~~ of said test compound;

c) selecting a compound that ~~modulates~~ inhibits the activity or expression of MSH5; and

d) identifying said selected compound as ~~being~~ a candidate compound useful as a contraceptive.

24. **(Amended)** The method of claim ~~23~~13, wherein said compound is an antisense MSH5 nucleic acid molecule.

29. **(Amended)** The method of claim 13, wherein said compound ~~modulates~~ inhibits the activity of an MSH5 substrate.

30. **(Amended)** A method for identifying a candidate compound useful as a contraceptive, comprising:

a) contacting a cell expressing MSH5 with a test compound;

b) determining the expression of the MSH5 gene or the activity of MSH5 in the presence ~~and absence~~ of said test compound;

c) selecting a compound that ~~modulates~~ inhibits the expression of the MSH5 gene or the activity of MSH5; and

d) identifying said selected compound as ~~being~~ a candidate compound useful as a contraceptive.

31. **(Amended)** A method for identifying a candidate compound useful for ~~modulating~~ inhibiting chromosome synapsis ~~meiosis~~ in a cell, comprising:

a) contacting MSH5 with a test compound;

b) determining the activity of MSH5 in the presence ~~and absence~~ of said test compound;

c) selecting a compound that ~~modulates~~ inhibits the activity of MSH5; and

d) identifying said selected compound as ~~being~~ a candidate compound useful for ~~modulating~~ inhibiting chromosome synapsis ~~meiosis~~ in a cell.

32. **(Amended)** A method for identifying a candidate compound useful for ~~modulating~~ inhibiting chromosome synapsis ~~meiosis~~ in a cell, comprising:

a) contacting a cell expressing MSH5 with a test compound;

b) determining the expression of the MSH5 gene or the activity of MSH5 in the presence ~~and absence~~ of said test compound;

c) selecting a compound that ~~modulates~~ inhibits the expression of the MSH5 gene or the activity of MSH5; and

d) identifying said selected compound as ~~being~~ a candidate compound useful for ~~modulating~~ inhibiting chromosome synapsis ~~meiosis~~ in a cell.

New claims 33-69 have been added as follows:

33. **(New)** The method of claim 32, wherein said cell is an oocyte or a spermatocyte.

34. **(New)** A method for identifying a candidate compound capable of preventing fertilization in a subject comprising:

a) contacting MSH5 with a test compound; and

b) assaying for modulation of the expression or activity of MSH5 in the presence of said test compound, wherein inhibition of the expression or activity of MSH5 by the

test compound identifies the test compound as a candidate compound capable of preventing fertilization in a subject.

35. **(New)** A method for identifying a candidate compound capable of preventing fertilization in a subject comprising:

a) contacting a cell expressing MSH5 with a test compound;

b) assaying for modulation of the expression or activity of MSH5 in the presence of said test compound, wherein inhibition of the expression or activity of MSH5 by the test compound identifies the test compound as a candidate compound capable of preventing fertilization in a subject.

36. **(New)** A method for identifying a candidate compound useful as a contraceptive comprising:

a) contacting MSH5 with a test compound; and

b) assaying for modulation of the expression or activity of MSH5 in the presence of said test compound, wherein inhibition of the expression or activity of MSH5 by the test compound identifies the test compound as a candidate compound useful as a contraceptive.

37. **(New)** A method for identifying a candidate compound useful as a contraceptive comprising:

a) contacting a cell expressing MSH5 with a test compound;

b) assaying for modulation of the expression or activity of MSH5 in the presence of said test compound, wherein inhibition of the expression or activity of MSH5 by the test compound identifies the test compound as a candidate compound useful as a contraceptive.

38. **(New)** The method of claim 30, wherein said compound is an antisense MSH5 nucleic acid molecule.

39. **(New)** The method of claim 30, wherein said compound is a small molecule.

40. **(New)** The method of claim 30, wherein said compound is an MSH5 antibody.

41. **(New)** The method of claim 30, wherein said compound is a peptide.

42. **(New)** The method of claim 30, wherein said compound is a peptidomimetic.

43. **(New)** The method of claim 30, wherein said compound inhibits the activity of an MSH5 substrate.

44. **(New)** The method of claim 34, wherein said compound is an antisense MSH5 nucleic acid molecule.

45. **(New)** The method of claim 34, wherein said compound is a small molecule.

46. **(New)** The method of claim 34, wherein said compound is an MSH5 antibody.

47. **(New)** The method of claim 34, wherein said compound is a peptide.

48. **(New)** The method of claim 34, wherein said compound is a peptidomimetic.

49. **(New)** The method of claim 34, wherein said compound inhibits the activity of an MSH5 substrate.

50. **(New)** The method of claim 35, wherein said compound is an antisense MSH5 nucleic acid molecule.

51. **(New)** The method of claim 35, wherein said compound is a small molecule.

52. **(New)** The method of claim 35, wherein said compound is an MSH5 antibody.

53. **(New)** The method of claim 35, wherein said compound is a peptide.

54. **(New)** The method of claim 35, wherein said compound is a peptidomimetic.

55. **(New)** The method of claim 35, wherein said compound inhibits the activity of an MSH5 substrate.

56. **(New)** The method of claim 36, wherein said compound is an antisense MSH5 nucleic acid molecule.

57. **(New)** The method of claim 36, wherein said compound is a small molecule.

58. **(New)** The method of claim 36, wherein said compound is an MSH5 antibody.

59. **(New)** The method of claim 36, wherein said compound is a peptide.

60. **(New)** The method of claim 36, wherein said compound is a peptidomimetic.

61. **(New)** The method of claim 36, wherein said compound inhibits the activity of an MSH5 substrate.

62. **(New)** The method of claim 37, wherein said compound is an antisense MSH5 nucleic acid molecule.

63. **(New)** The method of claim 37, wherein said compound is a small molecule.

64. **(New)** The method of claim 37, wherein said compound is an MSH5 antibody.

65. **(New)** The method of claim 37, wherein said compound is a peptide.

66. **(New)** The method of claim 37, wherein said compound is a peptidomimetic.

67. **(New)** The method of claim 37, wherein said compound inhibits the activity of an MSH5 substrate.

68. **(New)** A method for identifying a candidate compound useful for stimulating chromosome synapsis in a cell, comprising:

a) contacting MSH5 with a test compound;

b) determining the activity of MSH5 in the presence of said test compound;

c) selecting a compound that stimulates the activity of MSH5; and

d) identifying said selected compound as a candidate compound useful for stimulating chromosome synapsis in a cell.

69. **(New)** A method for identifying a candidate compound useful for stimulating chromosome synapsis in a cell, comprising:

a) contacting a cell expressing MSH5 with a test compound;

b) determining the expression of the MSH5 gene or the activity of MSH5 in the presence of said test compound;

c) selecting a compound that stimulates the expression of the MSH5 gene or the activity of MSH5; and

d) identifying said selected compound as a candidate compound useful for stimulating chromosome synapsis in a cell.